Synthesis of reaction-ready 6,6'-biindole and 6,6'-biisatin via palladium(II)-catalysed intramolecular C-H functionalisation

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Keywords
ii, synthesis, catalysed, reaction, intramolecular, c, h, functionalisation, ready, 6, biindole, biisatin, via, palladium, CMMB

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Synthesis of reaction-ready 6,6′-biindole and 6,6′-biisatin via palladium(II)-catalysed intramolecular C–H functionalisation†

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The first synthesis of a 6,6′-biindole and 6,6′-biisatin scaffold is reported with the penultimate step being the formation of the di-heterocyclic ring by Pd(II)-catalysed intramolecular C–H functionalisation and Sandmeyer cyclisation, respectively.

Nature provides a rich source of biaryl compounds with significant biological activity1 and numerous methods exist for the synthesis of structurally diverse biaryls e.g. by transition-metal catalysis2,3 or oxidative coupling.4 As part of our ongoing investigations into the biological activities of homo- and hetero-dimeric aromatic systems4,5 we have been investigating biindoles as bioisosteres of binaphthyl units. In particular we are interested in privileged heterocyclic scaffolds having the potential for multiple functionalisations in often unreactive positions. Although the synthesis of symmetrical biindoles has been reported,6 symmetrical 6,6′-unreactive positions. Although the synthesis of symmetrical biindoles as bioisosteres of binaphthyl units. In particular we are interested in privileged heterocyclic scaffolds having the potential for multiple functionalisations in often unreactive positions. Although the synthesis of symmetrical biindoles has been reported,6 symmetrical 6,6′-biindoles and 6,6′-bisatins have no literature precedence. Herein we report the first synthesis of the symmetrical 6,6′-biindole 1 and 6,6′-biisatin 2 biaryl scaffolds with strategically positioned ‘reaction-ready’ functional groups in the 2-, 3- and usually unreactive 4-positions, upon which chemical libraries can be built in search of bioactive compounds (Fig. 1).

Bromide was selected for the reactive handles in the normally deactivated 4,4′-positions, thus, the key intermediate was bianiline 8,7 which allowed for a convergent synthesis to both targets. A 2,3-dicarboxylate substituent pattern on the indole nucleus8 also allowed for future derivatisation, while reducing the reactivity of these positions during subsequent aryl bromide reactions. Thus, 8 was synthesised via a modified procedure in six steps from commercially available 2,2′-biphenol 3, without the need for column chromatography in an overall yield of 52% (Scheme 1).9,10 Key was the selective nitration of 6, followed by protection of the phenolic groups to provide 7, which was further reduced under ultrasound in the presence of iron11 to afford bianiline 8.

Transition-metal-catalysed direct arylation via C–H insertion has undergone rapid development, and is still receiving significant attention.12 A recent report12d outlined the synthesis of indoles from simple anilines and alkynes via a Pd(II)-catalysed C–H activation using dioxygen, however, at the outset of our work, the only reports of a 2,3-disubstituted methyl ester indole via Pd(II)-catalysis involved an excess of Pd(OAc)₂ (2 equiv.).13 For cyclisation of 8 to biindole 1, a catalytic method tolerating an aryl bromide substituent was required. Thus, the synthesis of enaminone 10 via Michael addition of dimethyl acetylenedicarboxylate to aniline 7 allowed for the optimisation of Pd(II)-catalysed C–H insertion and intramolecular cyclisation via indole 11 (Scheme 2).14

Intriguingly, solvent plays an important role in the mechanism for reaction. In the case of the Pd(II)-cyclisation of enamines, it has not been discussed in detail, however, compounds of similar structure to 10 are capable of forming a stable six-membered intramolecular hydrogen bond (Scheme 3),15 preventing the orientation required for intramolecular cyclisation to indole 11. Proton transfer can occur, allowing for both an enaminone 10A and imino-enol 10B tautomer, with equilibrium shifted to favour 10A as solvent polarity increases.15 On the basis of the previous experiments (Scheme 2)14 we postulate that both DMA and acetonitrile can competitively H-bond to the N–H enamine proton, disrupting the stable six-membered ring conformer 10A and establishing an equilibrium with the desired 10AA enamine intermediate. However, DMA participates more aggressively in H-bonding (Scheme 3),16 and thus, 10AA is expected to predominate in DMA.

Thus, we postulate a similar mechanism to Jiao and co-workers,12d with an emphasis on the importance of a strong H-bond acceptor solvent such as DMA (Scheme 3). Acting as a Lewis-base donor,16 coordination of DMA sets up an equilibrium thought to favour the conformation of 10AA, and increases the nucophilelicity of the α-carbon and arene through weakening of the N–H bond. C–H insertion via electrophilic palladation12d of 10AA and reconjugation of the DMA stabilised cationic imine intermediate affords 10AB, with subsequent electrophilic aromatic substitution and re-aromatisation providing palladacycle 10AC. Reductive elimination of 10AC gives the desired indole 11, with the Pd(0) generated reoxidized by a Cu(II) salt. Alternatively, C–H activation via an electrophilic aromatic substitution reaction could preceede enaminone C–H insertion, especially in an electron-rich arene such as 10. However, in less electrophilic arenes, previous intramolecular isotope effect studies for

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Fig. 1 Reaction ready 6,6′-biindole 1 and 6,6′-bisatin 2 target scaffolds.
oxidative Pd(II)-catalysed conditions\textsuperscript{12d} support the formation of an enaminone intermediate analogous to \ref{Scheme 1}.

Only limited examples of this reaction using substrates with strongly deactivating and/or potentially labile functional groups have been reported\textsuperscript{12d} Therefore we examined the tolerance of our optimised conditions\textsuperscript{14} using two electron-deficient arenes (Scheme 4). Indole \ref{Scheme 1} was isolated in modest yield (35\%) and 5-bromo indole \ref{Scheme 1} in a poorer yield (18\%). A higher catalyst loading and 50 mol\% Cu(OAc)\textsubscript{2}/H\textsubscript{2}O as co-oxidant marginally increased the yield of indole \ref{Scheme 1} to 22\%. Although not optimised, these indolisation conditions tolerate electron-deficient and aryl bromide functional groups, and could be utilised in the synthesis of the 6,6'-biindole \ref{Scheme 1}.

Reaction of dimethyl acetylenedicarboxylate with bianiline \ref{Scheme 1} provided di-enaminone \ref{Scheme 1} in 71\% yield. Cyclisation via Pd(II)-catalysed oxidative coupling yielded 6,6'-biindole \ref{Scheme 1} in 22\% yield (Table 1, entry 1). The higher catalyst and oxidant loading of 30 mol\% (15 mol\%/enaminone) and 100 mol\% (50 mol\%/enaminone), respectively, was used to promote more efficient oxidation of generated Pd(0). Further optimisation through catalyst and oxidant loading (Table 1, entries 2 and 3) did not improve the yield of \ref{Scheme 1}. Excess Pd(OAc)\textsubscript{2} in air resulted in complete consumption of \ref{Scheme 1}, however, \ref{Scheme 1} could only be isolated in 8\% yield with multiple by-products formed. The observed product distribution was presumably a consequence

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thus, demonstrates the superiority of an oxidative catalytic method.\textsuperscript{17} 6,6′-Bisatin 2 was realised in high yield over two steps from bainilane 8 via the robust and well preceded Sandmeyer method (Scheme 5).\textsuperscript{18} Isonitrosoacetanilide 17 was prepared in good yield (74%), and subsequent heating of 17 in concentrated sulfuric acid allowed di-cyclisation to occur, with bisatin 2 isolated in 83% yield after precipitation on crushed ice, without the requirement for chromatography.

In conclusion, we have demonstrated the first syntheses of 6,6′-biheterocycles from a common bainilane intermediate. Both the 6,6′-bindole 1 and 6,6′-bisatin 2 represent scaffolds which contain ‘reaction-ready’ functionalities in previously unreactive positions of the benzene ring, while retaining the possibility for subsequent derivatisations on the heterocyclic ring.

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Notes and references


9 Although there is precedence for direct bromination of 3, reported yields range from 30%–83%; see ref. 10 for examples. In our hands, reaction of 3 with Br\textsubscript{2} in acetic acid resulted in multiple products requiring significant efforts to isolate the components. Our protection/deprotection strategy was high yielding, straightforward, and required no chromatography. Using an isopropyl protecting group gave a 94% yield for bromination after recrystallisation.


14 (a) Full details and discussion on the optimisation of this reaction are provided in the ESI\textsuperscript{*}; (b) see ESI\textsuperscript{*}† Table S1, entries 8 and 10.


17 The synthesis of 6,6′-bindole under a Bischler-type cyclisation was unsuccessful. This acid-catalysed cyclisation was more successful with electron-rich arene such as 3,5-dimethoxyaniline 9.


<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Oxidant (mol%)</th>
<th>Time/h</th>
<th>Yield\textsuperscript{a} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)\textsubscript{2} (30)</td>
<td>Cu(OAc)\textsubscript{2}:H\textsubscript{2}O (100)</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)\textsubscript{2} (20)</td>
<td>Cu(OAc)\textsubscript{2}:H\textsubscript{2}O (20)</td>
<td>29</td>
<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)\textsubscript{2} (30)</td>
<td>Cu(OTf)\textsubscript{2} (100)</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)\textsubscript{2} (400)</td>
<td>None</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yield. \textsuperscript{b}An additional 10 mol% Pd(OAc)\textsubscript{2} and 10 mol% Cu(OAc)\textsubscript{2} added after 23 h.

scheme 5

synthesis of 6,6-bisatin.